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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KARL BRUCE THOR

Appeal 2008-2979[1]
Application 10/049,427
Technology Center 1600

Decided: February 4, 2009

Before TONI R. SCHEINER, ERIC GRIMES, and
MELANIE L. MCCOLLUM, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 37-42 and 51-54, all the claims pending. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Heard January 13, 2009. The real party in interest is APBI Holdings, LLC, which is a subsidiary of Pharmaceutical Product Development, Inc.

STATEMENT OF THE CASE

"Several psychiatric drugs have been reported to have side effects of inhibiting ejaculation. Thus oral pharmacotherapy for premature ejaculation using . . . certain selective serotonin re-uptake inhibitor drugs has been studied as an alternative to behavioral therapy" (Spec. 2: 27-30). However, "[t]he daily or chronic use of conventional SSRIs . . . for such therapy may result in adverse effects . . . In addition, chronic or daily administration of conventional SSRIs is . . . burdensome[,]" as is "not experiencing benefit from a drug with a single, or the first, administration" (*id.* at 5: 26-33).

"The invention relates to methods for the prevention, treatment, or management of . . . premature ejaculation in men, by administering a therapeutically effective amount of [dapoxetine] a rapid-onset selective serotonin reuptake inhibitor, or a pharmaceutically acceptable salt thereof, on an as-needed basis shortly before sexual activity" (*id.* at 1: 6-10), "while avoiding priming doses" (*id.* at 19: 24-25).

Claim 37 is representative of the subject matter on appeal, and reads as follows:

37. A method of treating or managing sexual dysfunction in a mammal in need of treatment which comprises administering on an as-needed basis to the mammal a therapeutically effective amount of dapoxetine or a pharmaceutically acceptable salt thereof, wherein the sexual dysfunction is premature ejaculation, wherein the mammal is a human male, and wherein said administration of dapoxetine is effective for treating or managing premature ejaculation in the absence of priming doses.

The Examiner relies on the following evidence:

Robertson et al. (Robertson)	US 5,135,947	Aug. 4, 1992
Eli Lilly	ZA 930694	Feb. 1, 1993

R. M. Lane, *A critical review of selective serotonin reuptake inhibitor-related sexual dysfunction; incidence, possible aetiology and implications for management*, 11(1) Journal of Psychopharmacology 72-82 (1997).

Chris G. McMahon & Kamal Touma (McMahon), *Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies*, 161(6) J. Urol. 1826-1830 (1999).

In addition, Appellant relies on the following evidence:

Declaration of David A. Rivas, MD, originally submitted July 27, 2006, under the provisions of 37 C.F.R. § 1.132 (hereinafter "Declaration").

The Examiner rejected claims 37-42 and 51-54 under 35 U.S.C. § 103(a) as unpatentable over McMahon and Lane in view of Eli Lilly and Robertson.

We reverse.

ISSUE ON APPEAL

The issue raised by this appeal is whether the Examiner has established that it would have been obvious for one skilled in the art to use the selective serotonin reuptake inhibitor, dapoxetine, on an as-needed basis, to treat premature ejaculation.

FINDINGS OF FACT

FF1 Appellant claims a method of treating or managing premature ejaculation in human males by administering a therapeutically effective amount of the selective serotonin reuptake inhibitor, dapoxetine, on an as-needed basis, wherein the administration is effective in the absence of priming doses.

FF2 According to the Specification, "[t]he terms 'as-needed,' 'as-needed basis,' 'prn,' and 'prn dosing,' as used herein, mean administering a

therapeutically effective amount of [dapoxetine] . . . at a time interval sufficient to provide an improved therapeutic profile . . . in the prevention, treatment, or management of sexual dysfunction while avoiding priming doses, chronic administration, and/or overdosing" (Spec. 19: 20-25).

FF3 According to Dr. David A. Rivas, "[t]he concept of a priming dose refers to a prior dose of a drug that has not been cleared from the body at the time of administration of a subsequent dose of the drug" (Declaration ¶ 5).

FF4 The Examiner rejected claims 37-42 and 51-54 under 35 U.S.C. § 103(a) as unpatentable over McMahon and Lane in view of Eli Lilly and Robertson.

FF5 Lane teaches that the use of SSRI antidepressants is associated with various forms of sexual dysfunction, including orgasm dysfunction, erectile dysfunction, decreased sexual desire, and delayed ejaculation (Lane 72), and suggests that because of these side effects, "SSRIs may be of use in the management of premature ejaculation in males" (*id.* at 79, col. 1).

FF6 Lane also teaches that different SSRIs (e.g., paroxetine, sertraline, fluoxetine, and fluvoxamine) have different effects on the incidence of sexual dysfunction. Lane suggests that this is due to their differing effects on the reuptake of dopamine (Lane 76, col. 1-2). According to Lane, "[t]he high selectivity of paroxetine for serotonin reuptake relative to dopamine reuptake may mean that paroxetine causes a relatively higher incidence of sexual dysfunction than other SSRIs" (*id.* at 79, col. 2).

FF7 Lane suggests that "[t]he use of low doses on an as needed basis prior to intercourse [to treat premature ejaculation] is a possibility for

SSRIs such as fluvoxamine, paroxetine and sertraline which have half-lives of approximately 1 day or less" (Lane 79, col. 2).

FF8 McMahon teaches that "[i]n the rat model the central neurotransmitter serotonin has an inhibitory effect on sexual function, while dopamine is generally stimulatory" and "[s]exual effects can occur through any shift in this serotonin-dopamine balance by an increase or decrease in either or both neurotransmitters" (McMahon 1826, col. 1).

FF9 McMahon evaluated the effects of administering paroxetine, a selective serotonin reuptake inhibitor, on premature ejaculation in normally potent men. In Study 1, the men received either 20 mg paroxetine or placebo as needed 3 to 4 hours before planned intercourse, and their cases were reviewed every 2 weeks. In Study 2, the men received either 10 mg paroxetine daily for 2 weeks followed by 20 mg paroxetine as needed 3 to 4 hours before planned intercourse for a further 4 weeks, or placebo daily for 3 weeks followed by placebo as needed for 4 weeks, and their cases were reviewed every 2 weeks (McMahon 1827, col. 1).

FF10 According to McMahon,

> Study 1 demonstrated that within 1 to 2 weeks . . . paroxetine administered as needed prolonged the ejaculatory interval. This effect was significantly superior to that after 2 weeks of placebo as needed. Study 2 demonstrated that the improved ejaculatory control achieved with paroxetine daily was maintained with continued administration of the drug as needed. Furthermore, studies 1 and 2 demonstrated that ejaculatory control achieved with paroxetine as needed was significantly better if patients were initially treated with the drug daily.

(McMahon 1828, col. 1).

FF11 Further according to McMahon,

> Paroxetine as needed appeared to be more efficacious after initial chronic dosing. . . . As a result of first pass metabolism, which is almost exclusively mediated by the P450 2D6 enzyme, the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract. However, paroxetine is also a potent inhibitor of this enzyme, thereby effectively inhibiting its own metabolism and demonstrating nonlinear pharmacokinetics. Therefore, as paroxetine concentration increases with multiple dosing, the P450 2D6 activity decreases and, thus, prolongs drug clearance and results in a disproportionately greater increase in concentration with every dose.

(McMahon 1829, col. 1-2 (internal citations omitted).)

FF12 Eli Lilly discloses "a use of fluoxetine/lovan, dapoxetine, duloxetine, amersergide, 228729, and zatosetron, to treat tobacco withdrawal symptoms" (Eli Lilly 1), as well as hundreds of additional cravings, disorders, diseases, symptoms, phobias, and conditions (*id.* at 1-8), including premature ejaculation (*id.* at 8).

FF13 Eli Lilly does not disclose a method of administering any of the compounds, nor does the reference disclose their effects on dopamine reuptake, or their pharmacokinetic properties.

FF14 Robertson discloses dozens of specific 1-phenyl-3-naphthalenyloxypropanamine compounds, "which are selective inhibitors of serotonin uptake" (Robertson, col. 1, ll. 36-38), including dapoxetine (N,N-Dimethyl-1-(3-methoxyphenyl)-3-(1-naphthalenyloxy)propanamine) (*id.* at col. 3, ll. 35-36).

FF15 Robertson teaches that the compounds "have a prolonged duration of action, and therefore are capable of inhibiting the uptake of

serotonin for an extended period of time" (*id.* at col. 19, ll. 25-28), and might be useful in treating "physiologic functions . . . subject to influence by brain serotoninergic neural systems . . . such as obesity, depression, alcoholism, pain, loss of memory, anxiety and smoking" (*id.* at col. 19, ll. 35-41).

PRINCIPLES OF LAW

"In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, ___, 127 S.Ct. 1727, 1739 (2007).

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103.

Id. at ___, 127 S.Ct. at 1742.

ANALYSIS

The Examiner concluded that "substituting the SSRIs as disclosed by McMahon and Lane with another SSRI, specifically dapoxetine" (Ans. 11), would have been "obvious to try" (*id.*), because McMahon teaches the use of paroxetine on an as-needed basis to treat premature ejaculation, "Lane

teaches the use of SSRIs broadly" (*id.*), and "Eli Lilly and Robertson disclose finite embodiments of SSRIs as known in the art" (*id.*), and "[t]herefore, a predictable potential solution to a recognized problem or need in the art had been identified" (*id.*).

Appellant acknowledges that "SSRIs were known to affect sexual function," but contends that "multiple compounds were being considered in the prior art for treatment of PE. . . . [and] the skilled person would not have had a reasonable expectation of success for the use of dapoxetine to effectively treat PE on an as-needed basis in the absence of priming doses without the benefit of hindsight using the Applicant's disclosure" (App. Br. 3). Appellant contends that the Examiner's reliance on an "obvious to try" rationale is misplaced (Reply Br. 6) because "it cannot be concluded that the use of dapoxetine would predictably solve the problem" (*id.*) of treating premature ejaculation on an as-needed basis in the absence of priming doses, thus, "the presently claimed invention does not meet those defined conditions of 'a finite number of identified, predictable solutions'" set out in *KSR* (*id.* at 3).

Appellant has the better argument. The evidence of record establishes that SSRIs have variable effects on sexual dysfunction (FF6), and that these variable effects are due in part to their different selectivities for serotonin and/or dopamine reuptake (FF6), as well as their different pharmacokinetics (FF11). For example, McMahon teaches that paroxetine exhibits non-linear pharmacokinetics, even when administered on an as-needed basis because of its ability to inhibit the enzyme that metabolizes it (FF11). That is, the effects of paroxetine intensify with multiple as-needed doses because its

clearance is prolonged, and its concentration disproportionately increased, as each successive dose of paroxetine cumulatively inhibits its own metabolism (FF10, 12). Eli Lilly, on the other hand, teaches "a use of" dapoxetine, and several other compounds, in treating hundreds of addictions, cravings, disorders, diseases, symptoms, phobias, and conditions, including premature ejaculation (FF12), but says nothing about any of the compounds' selectivity for serotonin and/or dopamine reuptake, how they should be administered, or their pharmacokinetics (FF13). Robertson mentions dapoxetine among dozens of other SSRIs (FF14), but does not mention premature ejaculation at all, and teaches that the compounds "have a prolonged duration of action" (FF15).

Thus, while the prior art may have identified a finite number of SSRIs, and taught that various SSRIs are associated with various sexual side effects, we agree with Appellant that the Examiner has not established that dapoxetine was known to have any of the properties that would have made it a predictable, obvious-to-try solution to the problem of treating premature ejaculation on an as-needed basis.

CONCLUSION OF LAW

The Examiner has not established that it would have been obvious for one skilled in the art to use the selective serotonin reuptake inhibitor, dapoxetine, on an as-needed basis, to treat premature ejaculation.

SUMMARY

We reverse the Examiner's rejection of 37-42 and 51-54 under 35 U.S.C. § 103(a) as unpatentable over McMahon and Lane in view of Eli Lilly and Robertson.

REVERSED

LP

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